REMARKS

Claims 1, 36, 82-87, and 90-93 have been amended. Claims 1, 11, 36, 42, 43, 82-88, and 90-93 are pending in the instant application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance.

I. The Rejection of Claims 1, 11, 36, 42, 43, 82-87, and 90-93 under 35 U.S.C. § 112, Second Paragraph

Claims 1, 11, 36, 42, 43, 82-87, and 90-93 stand rejected under 35 U.S.C. § 112, second paragraph, on the following grounds:

Ground 1: Claims 1, 11, 36, 42 and 43 stand rejected as being indefinite on the ground that the term "dissimilarity" is indefinite because the specification does not provide any criteria that defines how to determine whether something is dissimilar or not. This rejection is respectfully traversed for the reasons of record and further for the reasons stated below.

Applicants have pointed out in the Amendment of July 18, 2007, that the degree of similarity of the expression profiles is indicative of the similarity or dissimilarity of the mode of actions of the test compound and a known compound by comparison with hybridization with a second nucleic acid sample obtained from the bacterial cells cultured in the absence or presence of a standard compound having a known mode of action. Values are assigned to the hybridization complexes based on the relative amount of hybridization and the values are analyzed for the similarity or dissimilarity of the values to a second set of hybridization values assigned to the hybridization complexes formed from the second nucleic acid sample. The specification on page 22, lines 28-32, provides that, when comparing the actions of different antimicrobial compounds, similarity in the expression profile may mean that at least 1, preferably at least 5, more preferably at least 10, of the up-regulated arrayed genes commonly form hybridization complexes with the sample nucleic acid molecules at least once during a time course to a greater extent than would the nucleic acid molecules of a sample not treated with the test compound. The specification on page 22, lines 32-36, also provides that similarity can also mean that at least 1, preferably at least 5, more preferably at least 10, of the down-regulated nucleic acid molecules commonly form hybridization complexes with the arrayed genes at least once during a time course to a lesser extent than would the nucleic acid molecules of a sample not treated with the test compound or a known toxic compound. One of ordinary skill in the art would understand that if the degree of similarity of the expression profiles

does not fall within the limits of the definitions above, then the expression profiles are dissimilar. However, to further prosecution of the instant application, the claims have been amended to delete the term "dissimilarity".

Ground 2: Claims 82-87 stand rejected as being indefinite on the ground that the phrase "correspond to less than about 75% of the genome of the *Bacillus subtilis* cells" is a relative term and it is unclear how to define "corresponds to" since there is no definition for determining what sequences corresponds to the *B. subtilis* genome and which sequences do not correspond. This rejection is respectfully traversed.

The term "corresponds" is defined in Webster's New World Dictionary, Third College Edition of American English, as "to be similar, analogous, or equal to something". Applicants have substituted the term "corresponds to" in the claims with the term "equals".

Ground 3: Claim 36 stands rejected for reciting the limitation "the detected expression level" because there is insufficient antecedent basis. This rejection is respectfully traversed.

Claim 36 recites in part: "identifying from the plurality of nucleic acid sequences at least one sequence from the nucleic acid sample obtained from the *Bacillus subtilis* cells cultivated in the presence of the antimicrobial compound that has a detected expression level that is significantly different from the nucleic acid sample obtained from *Bacillus subtilis* cells cultivated in the absence of the antimicrobial compound, wherein the difference in the detected expression level is at least about 10% or greater." Consequently, the limitation "the detected expression level" has an antecedent basis in the claim.

Ground 4: Claims 90-93 stand rejected as being indefinite on the ground that the phrase "at least about 20, 50, 75 or 100% of the genome of the *Bacillus subtilis* cells" is a relative term and it is unclear how to define "at least about" since there is no definition for determining what is at least 20% and what is also about 20%.

Applicants have amended claims 90-93 to recite "about" in place of "at least about".

For the foregoing reasons, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 112 and respectfully request reconsideration and withdrawal of the rejections.

II. The Rejection of Claims 82-87 under 35 U.S.C. § 112, First Paragraph

Claims 82-87 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action stated:

> Applicants urge that page 13, lines 20-27 provide support for the plurality of sequences correspond to less than about 75%, 50%, 25%, 10%, 5%, or 2% of the genome of the *B. subtilis* cells. However, page 13, lines 20-27 that the sequences represent about 75% of the genome or less, about 50% of the

> genome or less, about 25% of the genome or less, about 10% of the genome or less, about 5% of the genome or less, or even about 2% of the genome or less. There is no teaching of the sequences corresponding to less than about 75%, 50%, 25%, 10%, 5%, or 2% of the genome of the *B. subtilis* cells. Therefore the rejection is maintained and applicants' arguments are not persuasive.

This rejection is respectfully traversed for the reasons of record.

Applicants have amended claims 82-87 to recite "about 75% of the genome or less", "about 50% of the genome or less", "about 25% of the genome or less", "about 10% of the genome or less", "about 5% of the genome or less", or "about 2% of the genome or less". Support for the amendment of claims 82-87 appears on page 13, lines 20-27, of the specification.

For the foregoing reasons, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 112 and respectfully request reconsideration and withdrawal of the rejections.

III. The Rejection of Claims 1, 11, 34, 36, and 42 under 35 U.S.C. § 103

Claims 1, 11, 34, 36, and 42 under 35 U.S.C. § 103 as being unpatentable over Wilson *et al.* (*PNAS* 96: 12833-12838, 1999) in view of Cao *et al.* (*Mol. Microbiol.* 45: 1267-1276, 2002). The Office Action stated:

> [I]t would have been prima facie obvious at the time of applicants' invention to apply the *Bacillus subtilis* strain of Cao et al., to Wilson et al., method for determining the mode of action of an antimicrobial compound in order to provide obtain antimicrobial mode of action results for *B. subtilis* which is known to be resistant to known antimicrobial drugs. One of ordinary skill in the art would have a reasonable expectation of success by exchanging one gram positive bacterium for another gram positive bacteria because both bacteria are known in the art to have analyzed on DNA microarrays wherein the hybridization complexes detected in the presence of antimicrobial compounds. Furthermore, no more than routine skill would have been required to exchange the *M. tuberculosis* of Wilson et al., for the *B. subtilis* of Cao et al., since the ability for pathway characterization is available because complete genome sequences of *B. subtilis* is known along with microarrays containing representatives of each of the genes. Finally it would have been prima facie obvious to combine the invention of Wilson et al., and Cao et al., to advantageously achieve a determining drug-induced alterations in gene expression by microarray hybridization for multi-drug resistant bacteria.

This rejection is respectfully traversed.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under 35 U.S.C. § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the *claimed subject matter as*

a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. John Deere*, 383 U.S. 1 (1966).

Wilson *et al.* disclose exploring drug-induced alterations in gene expression in *Mycobacterium tuberculosis* by microarray hybridization.

Cao *et al.* disclose antibiotics that inhibit cell wall biosynthesis induce expression of the *Bacillus subtilis* σ^W and σ^M regulons.

It is well established that focusing on individual elements of the claimed invention, rather than on the invention as a whole, is not the proper test under 35 U.S.C. § 103. *Environmental Designs v. Union Oil Co. of Cal.*, 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983). The critical inquiry is whether "there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." *Lindemann Maschinefabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d at 1462, 221 USPQ at 448.

Applicants submit that Wilson *et al.* and/or Cao *et al.* do not teach or suggest the instant invention. Wilson *et al.* teach the use of DNA microarrays to characterize the global transcriptional response of *Mycobacterium tuberculosis* to isoniazid (INH) at concentrations of 0.2 µg or 1 µg of INH per ml, which are above the minimum inhibitory concentration of INH, *i.e.*, 0.02 µg of INH per ml (see Argyrou *et al.*, 2006, *Nature Structural & Molecular Biology* 13: 408-413 [attached], which cites Bernstein *et al.*, 1952, *Am. Rev. Tuberc.* 65: 357-364 and Youatt, 1969, *Am. Rev. Respir. Dis.* 99: 729-749). Cao *et al.* teach the use of DNA microarrays to characterize the global transcriptional response of *Bacillus subtilis* to vancomycin at concentrations 10X the minimum inhibitory concentration (see page 1269, column 2, last paragraph). In both cases, sub-inhibitory concentrations are not used. The methods of the instant invention are particularly advantageous because they utilize sub-inhibitory amounts of an antimicrobial compound to more readily identify primary effects of the antimicrobial compound on genes of the bacterial cell and reduce secondary effects on other genes that can result from using high inhibitor concentrations of the compound. The use of sub-inhibitory concentrations slows the action of the compounds, and limits the expression of genes which are correlated to secondary stress induced proteins, allowing a predominance of expressed nucleic acids which correlate with the activity of the antimicrobial compound which is related directly, and primarily, with its mode of action on the cell.

Consequently, Wilson *et al.* and/or Cao *et al.* do not teach or suggest a method for determining the mode of action of an antimicrobial compound, comprising: (a) detecting hybridization complexes formed by contacting at least one nucleic acid sample, obtained by culturing cells of a *Bacillus subtilis* in the presence of at least one sub-inhibitory amount of an

antimicrobial compound having an unknown mode of action, with a plurality of nucleic acid sequences corresponding to genes of the *Bacillus subtilis* cells, wherein the plurality of nucleic acid sequences is contained on a substrate, wherein the presence, absence or change in the amount of the hybridization complexes detected, compared with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the *Bacillus subtilis* cells cultured in the absence or presence of a standard compound having a known mode of action, is indicative of the similarity of the mode of actions of the antimicrobial compound and the standard compound; and (b) assigning a mode of action for the antimicrobial compound based on the similarity of values assigned to the hybridization complexes detected in (a) based on the relative amount of hybridization to a second set of hybridization values assigned to the hybridization complexes formed from the second nucleic acid sample, as claimed herein.

For the foregoing reason, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 103 and respectfully request reconsideration and withdrawal of the rejections.

III. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: February 5, 2008

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